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THE UNITED STATES OF AMERICA

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February 07, 2005

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APPLICATION NUMBER: 60/535,908

FILING DATE: *January 12, 2004*

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Certified by

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Provisional Application Cover Sheet

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This is a request for filing a PROVISIONAL APPLICATION under 37 C.F.R. § 1.53(b)(2).

Docket Number: Q3399		Type a plus sign (+) inside this box		+
Inventor(s)/Applicant(s)				
Last Name	First Name	Middle Initial	Residence (City and either State or Foreign Country)	
Siegel Winey	Steven Karen		Berwyn, PA Philadelphia, PA	
Title of the Invention (280 Characters Maximum)				
A Long-Term Biodegradable Formulation for Risperidone and 9-oh-risperidone				
Correspondence Address				
University of Pennsylvania Center For Technology Transfer 3160 Chestnut Street Suite 200				
City: Philadelphia	State: Pennsylvania	Zip Code: 19104 - 6283	Country: US	
Enclosed Application Parts: (check all that apply)				
[X] Specification Number of pages: 16 [] Small Entity Statement				
[] Drawing(s) Number of sheets: [] Other (specify)				
Method of Payment (check one)				
[] Our Check No. _____ is enclosed to cover the Provisional filing fees. A duplicate copy of this sheet is enclosed.			Provisional Filing Fee Amount (\$)	\$ 80.00
[X] The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 13-2489. A duplicate copy of this sheet is enclosed.				
[] Payment by credit card. Form PTO-2028 is attached.				

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No

[] Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

Signature:

Typed or Printed Name: Steven Siegel

Date:

11/9/04

[] Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

22154 U.S. PTO
60/535908

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PROVISIONAL APPLICATION SUBMISSION TO USPTO – CONTENTS PAGE

Penn Docket Number : Q3399
First-named Inventor : Siegel
Submission Date : 1/12/04
Prepared by : Matt Thomas

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Total Number of Pages : 16

Siegel, S. J. et. al. Risperidone and 9-OH Risperidone

Brief Summary

We have devised a long-term delivery formulation for the antipsychotic agent risperidone and its active metabolite 9-oh-Risperidone. Risperidone is currently in use for the treatment schizophrenia, bipolar disorder, Alzheimer's Disease, psychotic depression, and other mental conditions that cause confusion, disorganization and psychosis. The current formulation would allow for incorporation of both risperidone and 9-oh-risperidone into multiple delivery platforms including:

1. Surgically implantable formulation: this method would be best suited for the treatment of chronic conditions listed above.
2. Incorporation into nanoparticles for stealth long-term delivery through the GI tract. As PLGA loaded nanoparticles are delivered across the intestinal mucosa, active drug would evade first pass metabolism. Additionally, this method could deliver antipsychotic activity for one-week interval.
3. The use of 9-oh-risperidone is included since this molecule has a hydroxyl functional group that allows for ester bond formation, and creation of pro-drug polymers that will deliver improved controlled release as compared to physical mixtures.

Stage of development

We have tested multiple compounds in PLGA delivery systems in vitro. These studies indicate that every drug results in a different pattern of release. Risperidone and 9-oh risperidone result in a highly stable drug-polymer matrix with kinetics that approach steady state over the delivery interval, even with a polymer (50:50 PLGA) that traditionally yields a high degree of drug dumping after an initial lag. Additionally, we are able to make nanoparticles with PLGA and incorporate drugs into these particles for oral delivery systems.

Applications/Commercial use

The commercial application of this technology is related to treatment of schizophrenia, bipolar disorder, Alzheimer's Disease, psychotic depression, and other mental conditions that cause confusion, disorganization and psychosis.

Closest know similar technology

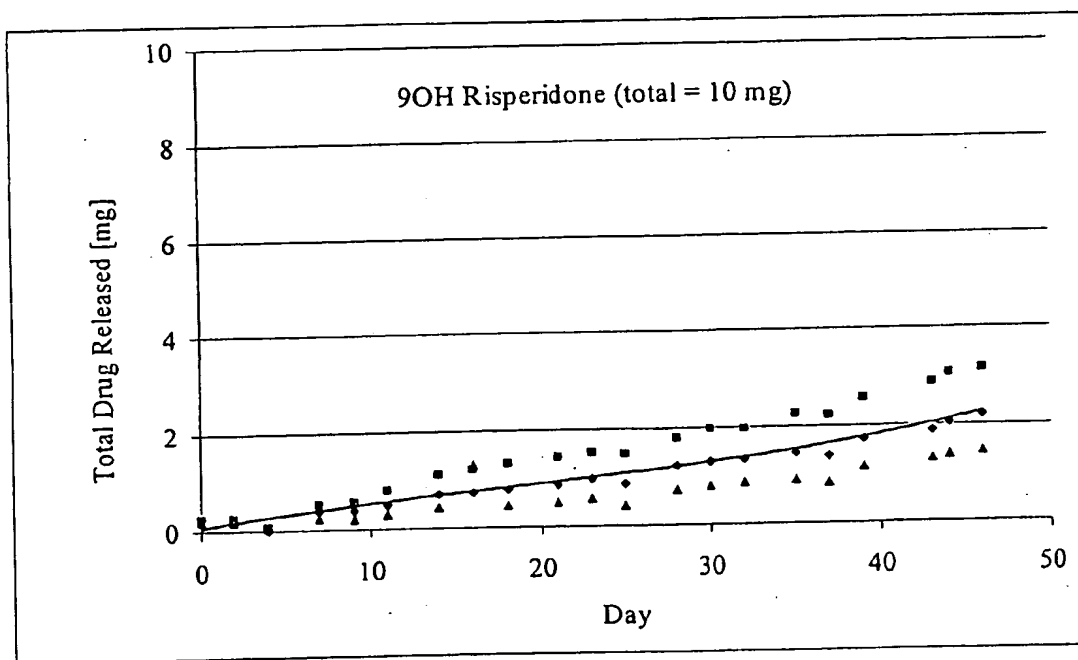
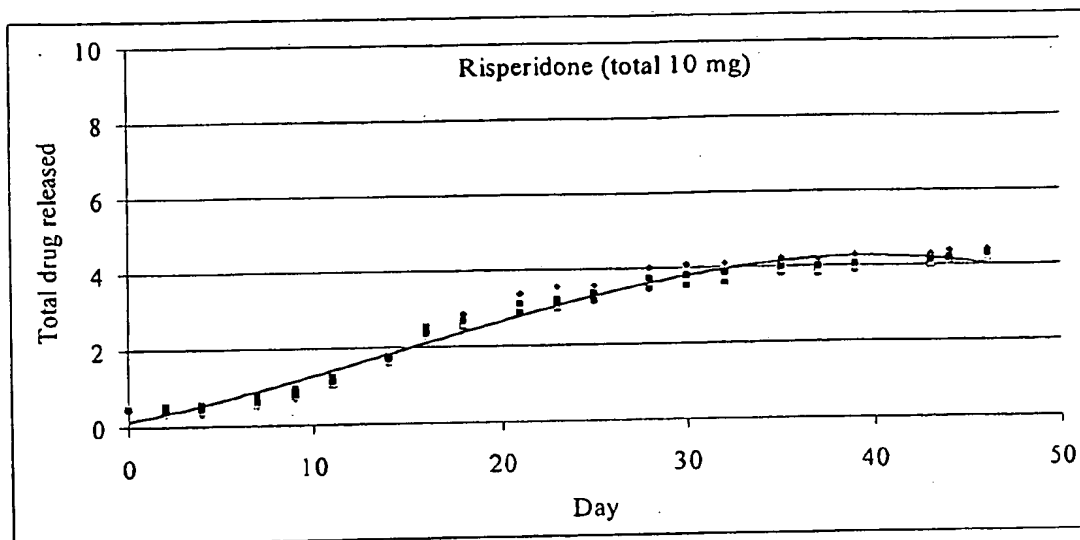
Current formulations of risperidone include daily oral formulations and biweekly PLGA based microspheres (Risperidone Consta). There are no pro-drug polymers utilizing 9-oh risperidone in use, or that we are aware of in development.

Differences / advantages

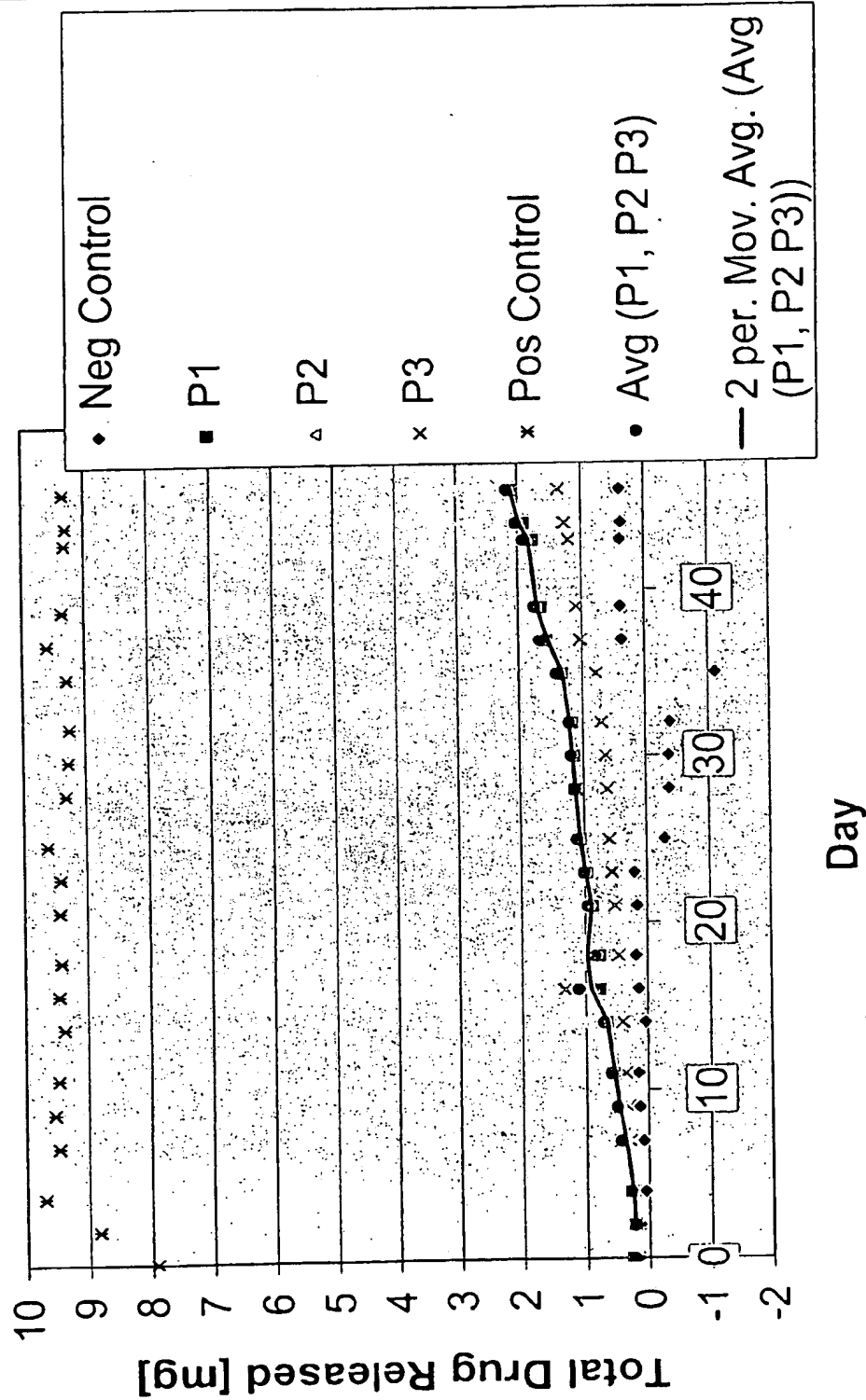
The major advantages to a long-term polymer based delivery system for this drug include:

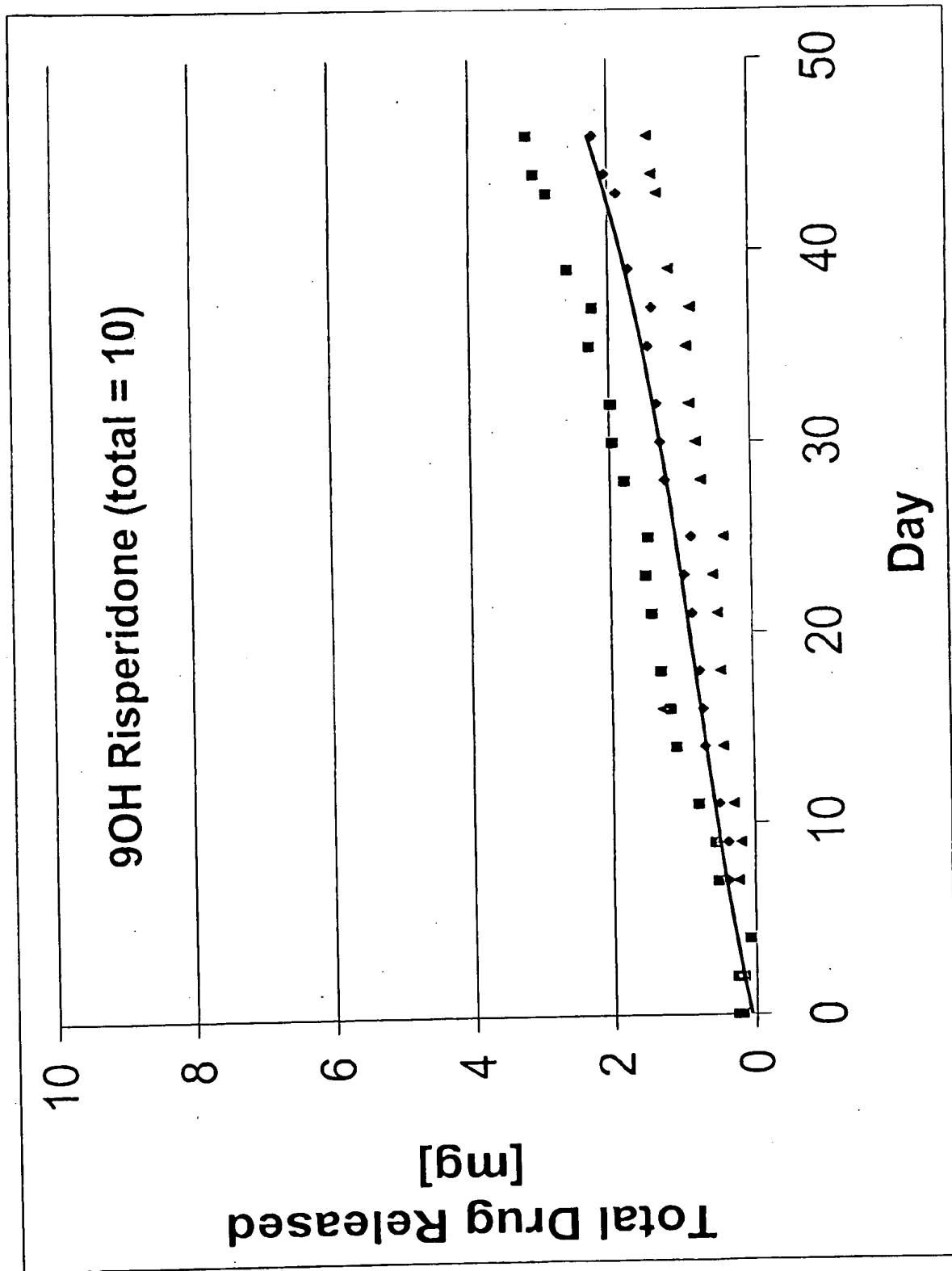
- Steady state delivery over weeks to months, avoiding peaks and troughs from oral dosing

- Lower dosing through avoidance of first pass metabolism resulting in less systemic toxicity.
- Greater ease of administration with resulting in improved adherence as compared to current oral medications.
- Long term implants t offer a degree of treatment adherence (annual) and resulting improvement that is not currently available in any psychiatric medication.



20% 85:15 90H



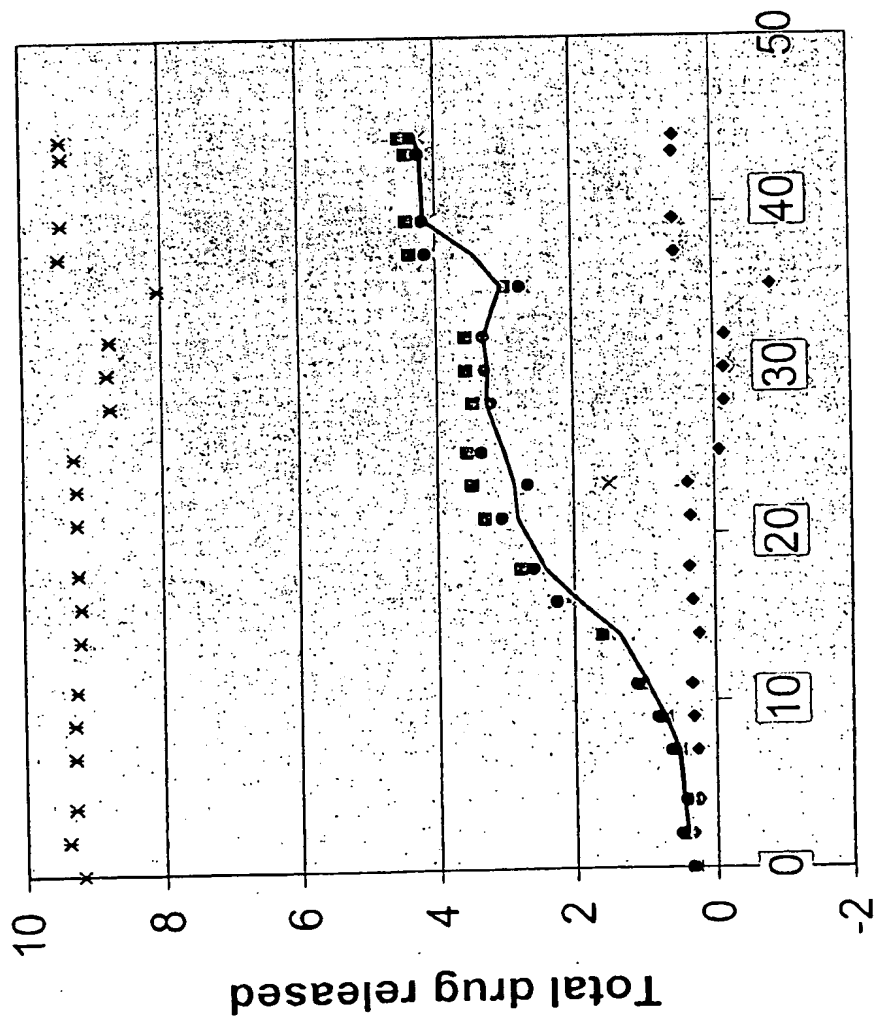


ABSORBANCE Day	Neg Control ABS	P1 ABS	P2 ABS	P3 ABS	Pos Control ABS	ABSORBANCE Day	Pos Control Correction Coefficient ABS	P1C Conc	P2C Conc	P3C Conc	Avg (P1, P2, P3) Conc
0	0	0	0.004	0.004	0.001	0					
2	-0.001	0.002	0.004	0.004	0	2	0.014	-0.009	-0.005	-0.012	-2.7034E-06
4	-0.005	0.005	0.009	0.009	0	4	0.003	0.010	0.017	0.003	0.000754258
7	-0.005	0.013	0.02	0.02	0.006	7	0.006	0.010	0.019	0.001	0.000754258
8	-0.002	0.016	0.025	0.025	0.007	9	0.003	0.016	0.031	0.006	0.000754258
11	-0.001	0.019	0.034	0.034	0.009	11	-0.002	0.026	0.046	0.013	0.001467722
14	-0.007	0.024	0.044	0.044	0.011	14	0.002	0.027	0.050	0.035	0.001467722
16	-0.002	0.029	0.052	0.052	0.057	16	0.000	0.029	0.056	0.014	0.001467722
18	0	0.029	0.056	0.056	0.014	18	0.001	0.034	0.062	0.016	0.001467722
21	-0.001	0.035	0.063	0.063	0.017	21	0.000	0.039	0.066	0.019	0.001467722
23	-0.023	0.044	0.074	0.074	0.021	23	0.000	0.034	0.064	0.011	0.001467722
25	-0.027	0.047	0.075	0.075	0.022	25	-0.005	0.052	0.080	0.027	0.001467722
28	-0.027	0.048	0.081	0.081	0.023	28	-0.007	0.055	0.088	0.030	0.001467722
30	-0.028	0.049	0.081	0.081	0.026	30	-0.008	0.057	0.089	0.034	0.001467722
32	-0.054	0.057	0.097	0.097	0.03	32	-0.006	0.063	0.103	0.036	0.001467722
35	0.009	0.069	0.11	0.11	0.042	35	0.009	0.060	0.101	0.033	0.001467722
37	0.01	0.073	0.115	0.115	0.045	37	-0.003	0.076	0.118	0.048	0.001467722
39	0.01	0.079	0.128	0.128	0.051	39	-0.005	0.084	0.133	0.056	0.001467722
43	0.009	0.085	0.136	0.136	0.054	43	-0.006	0.092	0.142	0.060	0.001467722
44	0.01	0.096	0.143	0.143	0.059	44	-0.004	0.100	0.147	0.063	0.001467722
46						46					

CONCENTRATION Day	Neg Control Conc	P1 Conc	P2 Conc	P3 Conc	Pos Control Conc	CONCENTRATION Day	P1C Conc	P2C Conc	P3C Conc	Avg (P1, P2, P3) Conc
0	0.000348743	0.00051095	0.0005109	0.0003893	0.015639418	0				
2	0.000308191	0.00042985	0.0005109	0.0003487	0.017664234	2	-1.62296E-05	0.00146	-0.00014	-2.7034E-06
4	0.000105434	0.0005515	0.0007137	0.0004298	0.018407948	4	0.000754258	0.001038	0.00047	0.000754258
7	0.000145985	0.00087591	0.0011598	0.0005921	0.018961882	7	0.000754258	0.001119	0.000389	0.000754258
9	0.00026764	0.00099757	0.0013625	0.0006328	0.019083536	9	0.000997567	0.001606	0.000592	0.001065153
11	0.000308191	0.0011922	0.0017275	0.0007137	0.018961882	11	0.001403082	0.002214	0.000876	0.001467722
14	6.48824E-05	0.00132198	0.002133	0.0007948	0.018759124	14	0.001443633	0.002376	0.002579	0.002133009
16	0.00026764	0.00152474	0.0024574	0.002602	0.01892133	16	0.001524738	0.00262	0.000916	0.001686942
18	0.000348743	0.00152474	0.0026198	0.0009165	0.018840227	18	0.001727494	0.002853	0.000998	0.001852666
21	0.000308191	0.00176805	0.0029035	0.0010381	0.018840227	21	0.001930251	0.003023	0.001119	0.002024872
23	0.000389294	0.0013301	0.0033496	0.0012003	0.019245742	23	0.001727494	0.002944	0.000795	0.001822114
25	-0.000583942	0.00211301	0.0033801	0.0012409	0.01863747	25	0.002457421	0.003317	0.001565	0.002687213
28	-0.000746148	0.00225466	0.0036334	0.0012814	0.018555367	28	0.002579075	0.003358	0.001444	0.002497972
30	-0.000746148	0.00233577	0.0036334	0.0014031	0.018515615	30	0.002687213	0.003358	0.001444	0.002497972
32	-0.000746148	0.00233577	0.0036334	0.0015633	0.018595918	32	0.002687213	0.003358	0.001444	0.002497972
35	-0.000746148	0.00233577	0.0036334	0.0015633	0.018595918	35	0.002687213	0.003358	0.001444	0.002497972
37	0.000713706	0.0031468	0.0048034	0.0020519	0.019205191	37	0.002781833	0.004444	0.001687	0.002871073
39	0.000754258	0.003399	0.0050122	0.0021735	0.018718573	39	0.00330657	0.005134	0.002295	0.003618897
43	0.000754258	0.003399	0.0050122	0.0021735	0.018718573	43	0.00330657	0.005134	0.002295	0.003618897
44	0.000713706	0.003399	0.0050122	0.0021735	0.018718573	44	0.00330657	0.005134	0.002295	0.003618897
46	0.000754258	0.003399	0.0050122	0.0021735	0.018718573	46	0.00330657	0.005134	0.002295	0.003618897

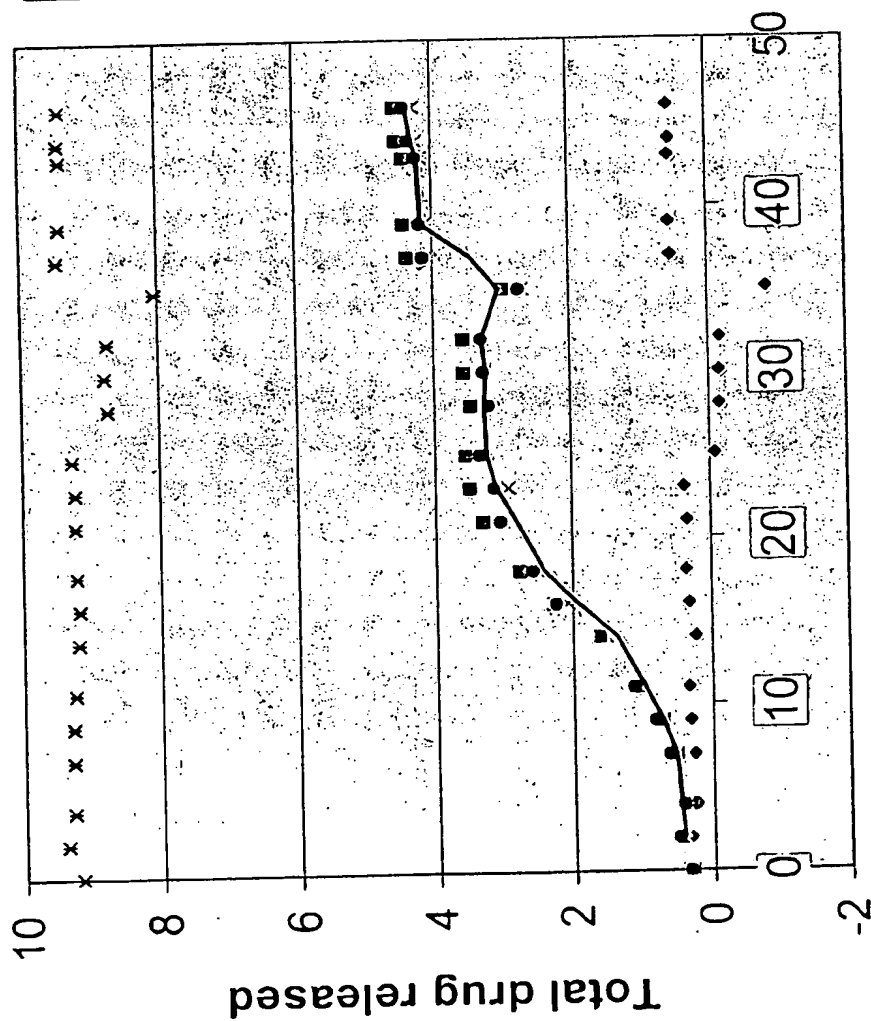
500 mL Corrected Day	Neg Control Total Drug	P1 Total Drug	P2 Total Drug	P3 Total Drug	Pos Control Total Drug	Avg (P1, P2, P3) Total Drug	500 mL Corrected Day	P1C Total Drug	P2C Total Drug	P3C Total Drug	Avg (P1, P2, P3) Total Drug
0	0.174371452	0.25547445	0.25547445	0.1946472	7.519708029	0.235198702	0	0.255474453	0.255474	0.194647	0.235198702
2	0.154095702	0.21492295	0.2554745	0.1743715	8.832116788	0.214922952	2	0.214922952	0.255474	0.174371	0.214922952
4	0.052716951	0.2757502	0.3568532	0.214923	9.703974047	0.262508786	4	-0.0081103	0.072993	-0.06894	-0.001351717
7	0.072982701	0.4379562	0.5798865	0.296026	9.480940795	0.437956204	7	0.377128954	0.519059	0.235199	0.377128954
9	0.133819951	0.49878345	0.6812852	0.3163017	9.541768045	0.498783455	9	0.377128954	0.559611	0.194647	0.377128954
11	0.154095702	0.55961071	0.863747	0.3566532	9.480940795	0.583403623	11	0.498783455	0.80292	0.296026	0.532575372
14	0.0324412	0.66098946	1.0665045	0.3974047	9.379562044	0.708299554	14	0.701540957	1.107056	0.437956	0.748851041
16	0.133819951	0.76236921	1.2287105	1.3300892	9.460665045	1.107055961	16	0.721816707	1.188159	1.289538	1.066504461
18	0.174371452	0.76236921	1.3098135	0.458232	9.420113544	0.843471208	18	0.863746959	1.431468	0.498783	0.843471208
21	0.154095702	0.86312571	1.4517437	0.5190592	9.403088204	0.951608543	21	0.863746959	1.512571	0.559611	0.931332793
23	0.194647202	0.96512571	1.512571	0.5596107	9.420113544	1.012435793	23	0.96512571	1.512571	0.559611	1.012435793
25	-0.291970803	1.06650446	1.674777	0.6001622	9.622871046	1.113815444	25	0.863746959	1.472018	0.397405	0.911057042
28	-0.373073804	1.12733171	1.6950527	0.620438	9.318734793	1.147607461	28	1.228710462	1.796431	0.721817	1.248986212
30	-0.353349554	1.16788321	1.8167072	0.6407137	9.278181293	1.201676129	30	1.289537713	1.958637	0.782844	1.34380638
32	-0.353349554	1.16788321	1.8167072	0.701541	9.257907543	1.228710462	32	1.330089213	1.978913	0.863747	1.390916464
35	-1.123276581	1.33008921	2.141182	0.782544	9.298459043	1.417950798	35	1.451743715	2.262774	0.904288	1.539605299
37	0.356653204	1.57339822	2.404704	1.025953	9.602555296	1.668018383	37	1.390916464	2.222222	0.843471	1.485536632
39	0.377128954	1.65450122	2.5060827	1.0867802	9.359286294	1.749121384	39	1.715328467	2.56691	1.147607	1.809948635
43	0.377128954	1.77615572	2.7696675	1.2084347	9.318734793	1.918085969	43	1.875334469	2.871046	1.309813	2.01946472
44	0.356653204	1.91808597	2.9318735	1.269262	9.298459043	2.03974047	44	2.03974047	3.053528	1.390916	2.161394972
46	0.377128954	2.12084347	3.0738037	1.3706407	9.339010543	2.188429305	46	2.201946472	3.154907	1.451744	2.269532396

20% 85:15 RISP



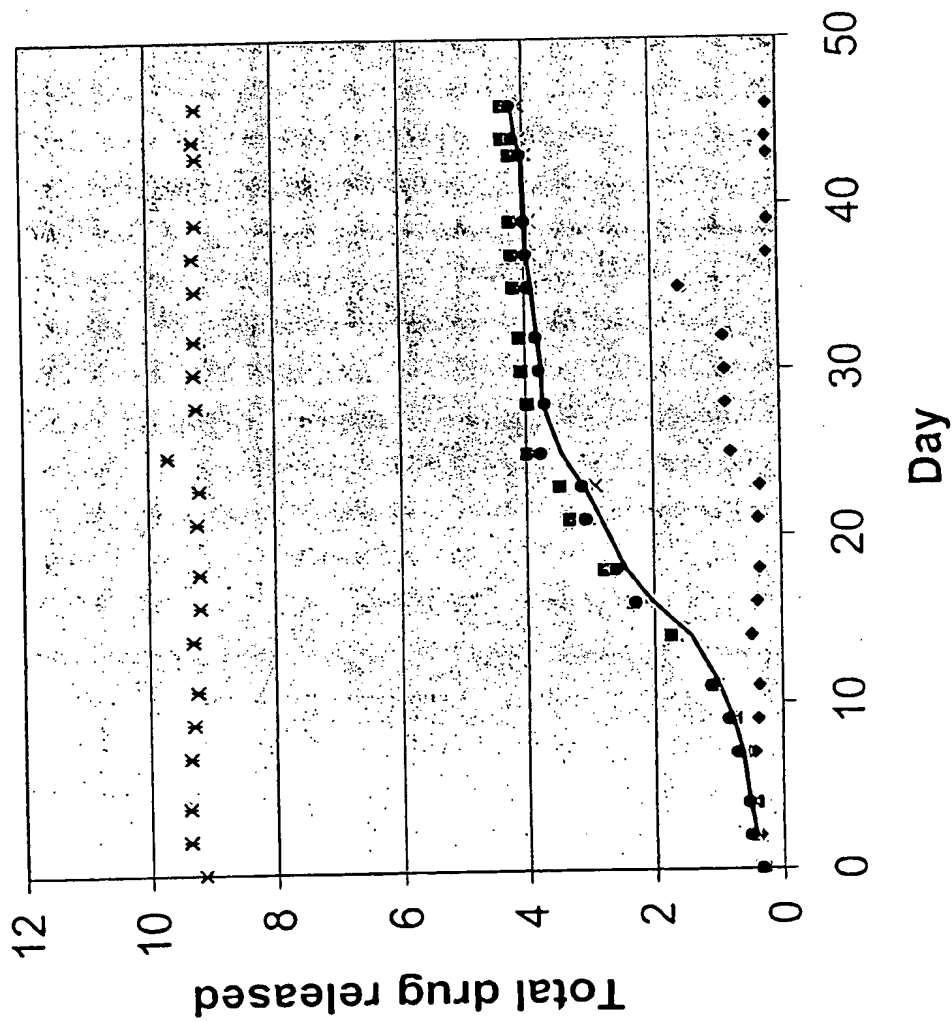
Day

20% 85:15 RISP {NEW}

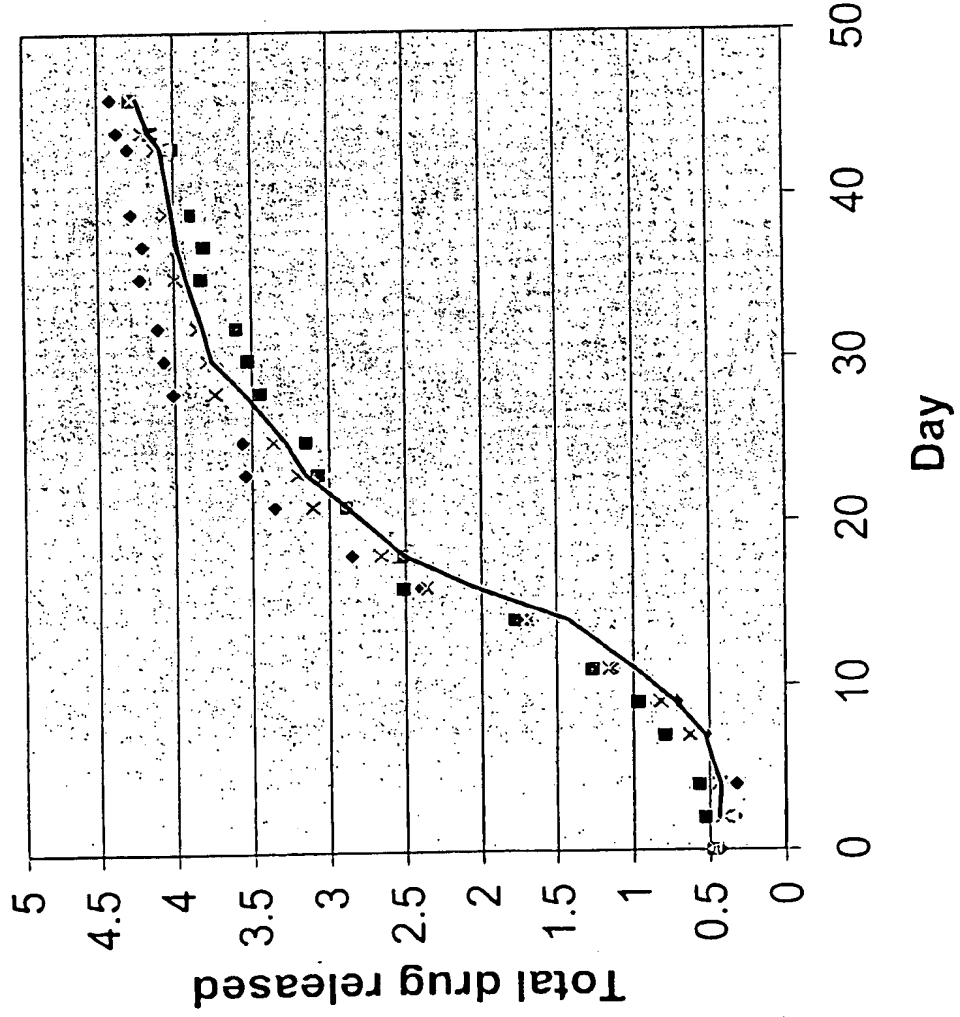


Day

20% 85:15 RISP {NEG CORRECTED}



20% 85:15 RISP {POS & NEG CORRECTED}



♦ P1C

■ P2C

▲ P3C

x Avg (P1C, P2C, P3C)

— 2 per. Mov. Avg. (Avg (P1C, P2C, P3C))

20% RISP 85:15

ABSORBANCE Day	Neg Control ABS	P1 Conc	P2 Conc	P3 Conc	Pos Control ABS	Pos Control ABS	new	ABSORBANCE Day	Neg Control ABS	P1 Conc	P2 Conc	P3 Conc	Pos Control ABS	Pos Control ABS
0	0	0	-0.002	0	0	0.468		0	0	-0.002	0	0	0	0.468
2	-0.001	0.004	0.014	0.005	0.005	0.479		2	-0.001	0.004	0.014	0.005	0.005	0.479
4	-0.006	-0.002	0.011	0.003	0.011	0.474		4	-0.006	-0.002	0.011	0.003	0.011	0.474
7	-0.005	0.009	0.023	0.011	0.023	0.474		7	-0.005	0.009	0.023	0.011	0.023	0.474
9	-0.002	0.019	0.032	0.022	0.032	0.474		9	-0.002	0.019	0.032	0.022	0.032	0.474
11	-0.001	0.038	0.046	0.035	0.046	0.472		11	-0.001	0.038	0.046	0.035	0.046	0.472
14	-0.007	0.066	0.07	0.062	0.062	0.469		14	-0.007	0.066	0.07	0.062	0.062	0.469
16	-0.002	0.102	0.108	0.091	0.108	0.468		16	-0.002	0.102	0.108	0.091	0.108	0.468
18	0	0.128	0.131	0.115	0.128	0.471		18	0	0.128	0.131	0.115	0.128	0.471
21	-0.001	0.156	0.166	0.141	0.156	0.471		21	-0.001	0.156	0.166	0.141	0.156	0.471
23	0.001	0.168	0.141	0.06	0.168	0.471		23	0.001	0.168	0.141	0.06	0.168	0.471
25	-0.023	0.169	0.147	0.159	0.169	0.473		25	-0.023	0.169	0.147	0.159	0.169	0.473
28	-0.027	0.165	0.135	0.151	0.165	0.445		28	-0.027	0.165	0.135	0.151	0.165	0.445
30	-0.027	0.17	0.141	0.154	0.17	0.447		30	-0.027	0.17	0.141	0.154	0.17	0.447
32	-0.028	0.17	0.143	0.156	0.17	0.445		32	-0.028	0.17	0.143	0.156	0.17	0.445
35	-0.064	0.139	0.118	0.124	0.139	0.408		35	-0.064	0.139	0.118	0.124	0.139	0.408
37	0.009	0.213	0.192	0.198	0.213	0.481		37	0.009	0.213	0.192	0.198	0.213	0.481
39	0.01	0.215	0.195	0.199	0.215	0.481		39	0.01	0.215	0.195	0.199	0.215	0.481
43	0.01	0.215	0.2	0.202	0.215	0.48		43	0.01	0.215	0.2	0.202	0.215	0.48
44	0.009	0.22	0.208	0.205	0.22	0.481		44	0.009	0.22	0.208	0.205	0.22	0.481
46	0.01	0.221	0.214	0.207	0.221	0.48		46	0.01	0.221	0.214	0.207	0.221	0.48

CONCENTRATION Day	Neg Control Conc	P1		P2		P3		Pos Control		Avg (P1, P2, P3)	mg/ml			
		Conc	Conc	Conc	Conc	Conc	Conc							
0	0.000715793	0.00064045	0.0007158	0.0007158	0.018346896	0.018346896	0.000630677	0	0.000716	0.00064	0.000716	0.000716	0.018347	0.000691
2	0.000678119	0.00066649	0.0012432	0.0009042	0.018761302	0.018761302	0.001004621	2	0.000678	0.000666	0.001243	0.000904	0.018761	0.001005
4	0.000489753	0.00064045	0.0011302	0.0008268	0.018572936	0.018572936	0.000856486	4	0.00049	0.00064	0.00113	0.000829	0.018573	0.000866
7	0.000527426	0.00105485	0.0015923	0.0011302	0.018572936	0.018572936	0.001255777	7	0.000527	0.001055	0.001592	0.00113	0.018573	0.001256
9	0.000640446	0.00143159	0.0019213	0.0015446	0.018572936	0.018572936	0.00183251	9	0.00064	0.001432	0.001921	0.001545	0.018573	0.001833
11	0.000678119	0.00214738	0.0024468	0.002072	0.018497569	0.018497569	0.00222725	11	0.000678	0.002147	0.002449	0.002072	0.018498	0.002223
14	0.00045208	0.00320223	0.0033529	0.0030515	0.018346896	0.018346896	0.00449568	14	0.000452	0.003202	0.003353	0.003052	0.018347	0.004496
16	0.000640446	0.00455947	0.0047845	0.0041441	0.018422242	0.018422242	0.005181242	16	0.00064	0.004559	0.004785	0.004144	0.018347	0.004496
18	0.000715793	0.00553787	0.0048975	0.0050482	0.018459916	0.018459916	0.0060277	18	0.000716	0.005538	0.004898	0.005048	0.018459	0.006161
21	0.000678119	0.00553787	0.005651	0.0060277	0.018459916	0.018459916	0.0060277	21	0.000678	0.005538	0.005651	0.006028	0.01846	0.006091
23	0.000753466	0.00696956	0.0060277	0.0060277	0.018459916	0.018459916	0.0060277	23	0.000753	0.00697	0.006028	0.005939	0.01846	0.006279
25	-0.000150693	0.00708256	0.0062538	0.006017	0.01853262	0.01853262	0.006017	25	-0.00015	0.007083	0.006254	0.006017	0.018535	0.006681
28	-0.000301388	0.00693168	0.0069017	0.006017	0.01748041	0.01748041	0.006379345	28	-0.0003	0.006932	0.006902	0.006017	0.01748	0.006379
30	-0.000301388	0.00712025	0.0061031	0.0065928	0.01748041	0.01748041	0.006555154	30	-0.00034	0.00712	0.006103	0.006593	0.01748	0.006555
32	-0.00033906	0.00712025	0.0051031	0.0065928	0.01748041	0.01748041	0.006603385	32	-0.00034	0.00712	0.006103	0.006593	0.01748	0.006555
35	-0.000695298	0.00595238	0.0051612	0.0053873	0.016086498	0.016086498	0.005500301	35	-0.0017	0.005952	0.005161	0.005387	0.016086	0.0055
37	0.001092526	0.00881155	0.008621	0.0081751	0.018911995	0.018911995	0.008288125	37	0.0010955	0.008816	0.008622	0.008175	0.018912	0.008288
39	0.001092526	0.00881155	0.008621	0.0081751	0.018911995	0.018911995	0.008288125	39	0.001093	0.008816	0.008622	0.008175	0.018912	0.008288
43	0.001092526	0.00881155	0.008621	0.0081751	0.018911995	0.018911995	0.008288125	43	0.001093	0.008816	0.008622	0.008175	0.018912	0.008288
44	0.001092526	0.00881155	0.008621	0.0081751	0.018911995	0.018911995	0.008288125	44	0.001093	0.008816	0.008622	0.008175	0.018912	0.008288
46	0.001092526	0.00881155	0.008621	0.0081751	0.018911995	0.018911995	0.008288125	46	0.001093	0.008816	0.008622	0.008175	0.018912	0.008288

corrected for negative control									
Day	neg control	P1	corrected	P2	corrected	P3	corrected	Pos control	Pos corrected
0	0	0	-0.002	0	0	0	0	0.468	0.468
2	0.001	0.005	0.015	0.006	0.006	0.006	0.006	0.48	0.48
4	0.006	0.004	0.017	0.009	0.009	0.009	0.009	0.48	0.48
7	0.005	0.014	0.028	0.016	0.016	0.016	0.016	0.479	0.479
9	0.002	0.021	0.034	0.024	0.024	0.024	0.024	0.476	0.476
11	0.001	0.039	0.047	0.037	0.037	0.037	0.037	0.473	0.473
14	0.007	0.073	0.077	0.069	0.069	0.069	0.069	0.476	0.476
16	0.002	0.104	0.111	0.093	0.093	0.093	0.093	0.47	0.47
18	0	0.128	0.131	0.115	0.115	0.115	0.115	0.47	0.47
21	0.001	0.157	0.132	0.142	0.142	0.142	0.142	0.472	0.472
23	-0.001	0.165	0.14	0.135	0.135	0.135	0.135	0.47	0.47
25	0.023	0.192	0.17	0.182	0.182	0.182	0.182	0.496	0.496
28	0.027	0.192	0.162	0.176	0.176	0.176	0.176	0.472	0.472
30	0.027	0.197	0.168	0.181	0.181	0.181	0.181	0.474	0.474
32	0.028	0.198	0.171	0.184	0.184	0.184	0.184	0.473	0.473
35	0.064	0.203	0.182	0.188	0.188	0.188	0.188	0.472	0.472
37	-0.009	0.204	0.183	0.189	0.189	0.189	0.189	0.474	0.474
39	-0.01	0.205	0.185	0.189	0.189	0.189	0.189	0.471	0.471
43	-0.01	0.205	0.19	0.192	0.192	0.192	0.192	0.47	0.47
44	-0.009	0.211	0.199	0.196	0.196	0.196	0.196	0.472	0.472
46	-0.01	0.211	0.204	0.197	0.197	0.197	0.197	0.47	0.47
								0.47419	0.47419

Corrected for Negative and Positive Control									
Day	Positive Correction Coefficient			P1C	P2C	P3C	Avg (P1C, P2C, P3C)		
0	-0.00619	0.00419	0.00619	0.00619	0.00619	0.00619	0.00619	0.00619	0.00619
2	0.00581	-0.00081	0.00081	0.00081	0.00081	0.00081	0.00081	0.00081	0.00081
4	0.00581	-0.00181	0.01119	0.01119	0.01119	0.01119	0.01119	0.01119	0.01119
7	0.00481	0.00919	0.02319	0.02319	0.02319	0.02319	0.02319	0.02319	0.02319
9	0.00181	0.01919	0.03219	0.03219	0.03219	0.03219	0.03219	0.03219	0.03219
11	-0.00119	0.04019	0.04819	0.04819	0.04819	0.04819	0.04819	0.04819	0.04819
14	0.00181	0.07119	0.07519	0.07519	0.07519	0.07519	0.07519	0.07519	0.07519
16	-0.00419	0.10819	0.11419	0.11419	0.11419	0.11419	0.11419	0.11419	0.11419
18	-0.00419	0.13219	0.11519	0.11519	0.11519	0.11519	0.11519	0.11519	0.11519
21	-0.00219	0.15919	0.13419	0.13419	0.13419	0.13419	0.13419	0.13419	0.13419
23	-0.00419	0.16919	0.14419	0.14419	0.14419	0.14419	0.14419	0.14419	0.14419
25	0.02181	0.17019	0.14819	0.14819	0.14819	0.14819	0.14819	0.14819	0.14819
28	-0.00219	0.19419	0.16419	0.16419	0.16419	0.16419	0.16419	0.16419	0.16419
30	-0.00019	0.19719	0.16819	0.16819	0.16819	0.16819	0.16819	0.16819	0.16819
32	-0.00119	0.19919	0.17219	0.17219	0.17219	0.17219	0.17219	0.17219	0.17219
35	-0.00219	0.20519	0.18419	0.18419	0.18419	0.18419	0.18419	0.18419	0.18419
37	-0.00019	0.20419	0.18319	0.18319	0.18319	0.18319	0.18319	0.18319	0.18319
39	-0.00319	0.20819	0.18819	0.18819	0.18819	0.18819	0.18819	0.18819	0.18819
43	-0.00419	0.20919	0.19419	0.19419	0.19419	0.19419	0.19419	0.19419	0.19419
44	-0.00219	0.21319	0.20119	0.20119	0.20119	0.20119	0.20119	0.20119	0.20119
46	-0.00419	0.21519	0.20819	0.20819	0.20819	0.20819	0.20819	0.20819	0.20819

CONCENTRATION									
Day	Conc	P1	Conc	P2	Conc	P3	Conc	Avg (P1, P2, P3)	Conc
0	0.000716	0.00064	0.000716	0.000716	0.000716	0.000716	0.000716	0.000716	0.000716
2	0.000753	0.000904	0.001281	0.000942	0.000942	0.000942	0.000942	0.000942	0.000942
4	0.000942	0.000866	0.001356	0.001055	0.001055	0.001055	0.001055	0.001055	0.001055
7	0.000904	0.001243	0.001771	0.001319	0.001319	0.001319	0.001319	0.001319	0.001319
9	0.000791	0.001507	0.001997	0.00162	0.00162	0.00162	0.00162	0.00162	0.00162
11	0.000753	0.002185	0.002486	0.00211	0.00211	0.00211	0.00211	0.00211	0.00211
14	0.00098	0.003468	0.003617	0.003315	0.003315	0.003315	0.003315	0.003315	0.003315
16	0.000781	0.004534	0.004466	0.004219	0.004219	0.004219	0.004219	0.004219	0.004219
18	0.000716	0.005538	0.004899	0.005048	0.005048	0.005048	0.005048	0.005048	0.005048
21	0.000753	0.006831	0.005689	0.005065	0.005065	0.005065	0.005065	0.005065	0.005065
23	0.000878	0.006932	0.00599	0.005602	0.005602	0.005602	0.005602	0.005602	0.005602
25	0.001582	0.007948	0.00712	0.007572	0.007572	0.007572	0.007572	0.007572	0.007572
28	0.001733	0.007949	0.006819	0.007422	0.007422	0.007422	0.007422	0.007422	0.007422
30	0.001733	0.008137	0.007045	0.007535	0.007535	0.007535	0.007535	0.007535	0.007535
32	0.001771	0.008175	0.007158	0.007648	0.007648	0.007648	0.007648	0.007648	0.007648
35	0.003127	0.008363	0.007572	0.007799	0.007799	0.007799	0.007799	0.007799	0.007799
37	0.000377	0.008401	0.00761	0.007836	0.007836	0.007836	0.007836	0.007836	0.007836
39	0.000379	0.008439	0.007685	0.007836	0.007836	0.007836	0.007836	0.007836	0.007836
43	0.000379	0.008439	0.007874	0.007949	0.007949	0.007949	0.007949	0.007949	0.007949
44	0.000377	0.008655	0.008213	0.0081	0.0081	0.0081	0.0081	0.0081	0.0081
46	0.000379	0.008655	0.008401	0.008137	0.008137	0.008137	0.008137	0.008137	0.008137

CONCENTRATION									
Day	P1C	P2C	P3C	Avg (P1C, P2C, P3C)	Conc	P1C	P2C	P3C	Avg (P1C, P2C, P3C)
0	0.000873544	0.000949	0.000949	0.000949	0.000949	0.000873544	0.000949	0.000949	0.000949
2	0.000685277	0.001062	0.000723	0.000723	0.000723	0.000685277	0.001062	0.000723	0.000723
4	0.000647604	0.001137	0.000836	0.000836	0.000836	0.000647604	0.001137	0.000836	0.000836
7	0.00106201	0.001589	0.001137	0.001137	0.001137	0.00106201	0.001589	0.001137	0.001137
9	0.001438743	0.001928	0.001552	0.001552	0.001552	0.001438743	0.001928	0.001552	0.001552
11	0.002229882	0.002531	0.002155	0.002155	0.002155	0.002229882	0.002531	0.002155	0.002155
14	0.003397755	0.003548	0.003247	0.003247	0.003247	0.003397755	0.003548	0.003247	0.003247
16	0.004791667	0.005018	0.004377	0.004377	0.004377	0.004791667	0.005018	0.004377	0.004377
18	0.005959826	0.005955	0.005206	0.005206	0.005206	0.005959826	0.005955	0.005206	0.005206
21	0.006713005	0.005771	0.006148	0.006148	0.006148	0.006713005	0.005771	0.006148	0.006148
23	0.007089738	0.006148	0.00596	0.00596	0.00596	0.007089738	0.006148	0.00596	0.00596
25	0.007127411	0.006299	0.006751	0.006751	0.006751	0.007127411	0.006299	0.006751	0.006751
28	0.00803157	0.006901	0.007504	0.007504	0.007504	0.00803157	0.006901	0.007504	0.007504
30	0.00814459	0.007052	0.007542	0.007542	0.007542	0.00814459	0.007052	0.007542	0.007542
32	0.008219537	0.007203	0.007693	0.007693	0.007693	0.008219537	0.007203	0.007693	0.007693
35	0.008445576	0.007655	0.007881	0.007881	0.007881	0.008445576	0.007655	0.007881	0.007881
37	0.008408303	0.007617	0.007843	0.007843	0.007843	0.008408303	0.007617	0.007843	0.007843
39	0.008558996	0.007806	0.007956	0.007956	0.007956	0.008558996	0.007806	0.007956	0.007956
43	0.00859667	0.008032	0.008107	0.008107	0.008107	0.00859667	0.008032	0.008107	0.008107
44	0.008747353	0.008235	0.008182	0.008182	0.008182	0.008747353	0.008235	0.008182	0.008182
46	0.008822709	0.008559	0.008295	0.008295	0.008295	0.008822709	0.008559	0.008295	0.008295

500 mL Corrected Day	Total Drug Neg Control	Total Drug P1	Total Drug P2	Total Drug P3	Total Drug Pos Control	Total Drug Avg (P1, P2, P3)	Total Drug in milligrams
0	0.357896	0.320223	0.357896	0.357896	9.173448	0.345336557	0.345336557
2	0.33906	0.433243	0.621609	0.45208	9.380650995	0.502310629	0.502310629
4	0.244876	0.320223	0.565099	0.414406	9.286467752	0.433242817	0.433242817
7	0.263713	0.527426	0.791139	0.565099	9.286467752	0.627888266	0.627888266
9	0.320223	0.715793	0.960669	0.772303	9.286467752	0.816254772	0.816254772
11	0.33906	1.073689	1.224382	1.036016	9.248794454	1.111362266	1.111362266
14	0.22604	1.601115	1.676462	1.525769	9.192264509	1.60111513	1.60111513
16	0.320223	2.279234	2.392254	2.072031	9.173448	2.247640064	2.247640064
18	0.357896	2.76997	2.448764	2.524111	9.21121157	2.50620856	2.50620856
21	0.33906	3.296414	2.825497	3.013864	9.229957806	3.045256188	3.045256188
23	0.376733	3.48478	3.013864	2.916881	9.229957806	2.662246333	2.662246333
25	-0.07535	3.54129	3.126884	3.352923	9.267631103	3.340355682	3.340355682
28	-0.15069	3.465943	2.900844	3.20223	8.740204943	3.169672453	3.169672453
30	-0.16953	3.560127	3.051537	3.296414	8.7787824	3.27576854	3.27576854
32	-0.84765	2.97619	2.590621	2.693641	8.740204943	3.302652385	3.302652385
35	0.527426	4.370102	3.974539	4.087553	8.043248945	2.750150593	2.750150593
37	0.546263	4.407776	4.031043	4.106389	9.416324292	4.144052688	4.144052688
39	0.546263	4.407776	4.031043	4.106389	9.416324292	4.181735985	4.181735985
43	0.527426	4.501959	4.275919	4.219409	9.399467643	4.231967048	4.231967048
44	0.546263	4.520796	4.388939	4.257083	9.418324292	4.332429174	4.332429174
46	0.546263	4.520796	4.388939	4.257083	9.399467643	4.38893912	4.38893912

500 mL Corrected Day	Total Drug Neg Control	Total Drug P1	Total Drug P2	Total Drug P3	Total Drug Pos Control	Total Drug Avg (P1, P2, P3)	Total Drug in milligrams
0	0.357896	0.320223	0.357896	0.357896	9.173448	0.345336557	0.345336557
2	0.33906	0.433243	0.621609	0.45208	9.380650995	0.502310629	0.502310629
4	0.244876	0.320223	0.565099	0.414406	9.286467752	0.433242817	0.433242817
7	0.263713	0.527426	0.791139	0.565099	9.286467752	0.627888266	0.627888266
9	0.320223	0.715793	0.960669	0.772303	9.286467752	0.816254772	0.816254772
11	0.33906	1.073689	1.224382	1.036016	9.248794454	1.111362266	1.111362266
14	0.22604	1.601115	1.676462	1.525769	9.192264509	1.60111513	1.60111513
16	0.320223	2.279234	2.392254	2.072031	9.173448	2.247640064	2.247640064
18	0.357896	2.76997	2.448764	2.524111	9.21121157	2.50620856	2.50620856
21	0.33906	3.296414	2.825497	3.013864	9.229957806	3.045256188	3.045256188
23	0.376733	3.48478	3.013864	2.916881	9.229957806	2.662246333	2.662246333
25	-0.07535	3.54129	3.126884	3.352923	9.267631103	3.340355682	3.340355682
28	-0.15069	3.465943	2.900844	3.20223	8.740204943	3.169672453	3.169672453
30	-0.16953	3.560127	3.051537	3.296414	8.7787824	3.27576854	3.27576854
32	-0.84765	2.97619	2.590621	2.693641	8.740204943	3.302652385	3.302652385
35	0.527426	4.370102	3.974539	4.087553	8.043248945	2.750150593	2.750150593
37	0.546263	4.407776	4.031043	4.106389	9.416324292	4.144052688	4.144052688
39	0.546263	4.407776	4.031043	4.106389	9.416324292	4.181735985	4.181735985
43	0.527426	4.501959	4.275919	4.219409	9.399467643	4.231967048	4.231967048
44	0.546263	4.520796	4.388939	4.257083	9.418324292	4.332429174	4.332429174
46	0.546263	4.520796	4.388939	4.257083	9.399467643	4.38893912	4.38893912

500 mL
Corrected Day

500 mL Corrected	Total Drug Neg Cont	Total Drug P1	Total Drug P2	Total Drug P3	Total Drug Pos Cont	Total Drug Avg (P1, P2, P3)	Total Drug Day
0	0.357896	0.320223	0.357896	0.357896	9.172448	0.345339	0
2	0.376733	0.45208	0.640446	0.470916	9.399488	0.521147	2
4	0.476916	0.433243	0.678119	0.574726	9.399488	0.546263	4
7	0.45208	0.621609	0.665322	0.659283	9.390651	0.722072	7
8	0.39557	0.753466	0.998342	0.809976	9.324141	0.853928	8
11	0.376733	1.092576	1.243219	1.054852	9.267631	1.130199	11
14	0.489753	1.732972	1.808318	1.657625	9.24141	1.732972	14
16	0.39557	2.316908	2.429928	2.109705	9.211121	2.285513	16
18	0.357896	2.788987	2.448764	2.524111	9.211121	2.580621	18
21	0.376733	3.15125	2.844334	3.0327	9.248794	3.064095	21
23	0.33908	3.465943	2.995027	2.900844	9.211121	3.120605	23
25	0.791139	3.974533	3.560127	3.765166	9.200874	3.773609	25
28	0.866486	3.974533	3.409433	3.71082	9.248794	3.698262	28
30	0.866486	4.068716	3.52453	3.76733	9.286468	3.765166	30
32	0.865322	4.087553	3.578963	3.82384	9.267631	3.830119	32
35	1.563442	4.181736	3.788166	3.899186	9.248794	3.955698	35
37	0.188366	4.200573	3.605003	3.918023	9.286468	3.974533	37
39	0.16953	4.219409	3.842676	3.918023	9.239958	3.993369	39
43	0.16953	4.219409	3.842676	3.918023	9.211121	4.043601	43
44	0.188366	4.332429	4.106389	4.049879	9.248794	4.162899	44
46	0.16953	4.332429	4.200573	4.068716	9.211121	4.200573	46
					9.290056		

P1C Total Drug	P2C Total Drug	P3C Total Drug	Avg (P1C, P2C, P3C) Total Drug
0.436821881	0.474495	0.474495	0.461937412
0.342536536	0.531005	0.361475	0.411706349
0.373801989	0.568678	0.417885	0.436821881
0.531005124	0.794718	0.568678	0.631467249
0.719371608	0.964248	0.775882	0.819833735
1.11494123	1.265634	1.077268	1.152614527
1.698877336	1.774224	1.623531	1.690877336
2.395833333	2.508653	2.18863	2.364438919
2.847912899	2.52769	2.603036	2.659546414
3.356502411	2.865586	3.073953	3.105347097
3.544688897	3.073953	3.879769	3.19653034
3.563705546	3.149299	3.315339	3.362781294
4.015785112	3.450686	3.752072	3.739514266
4.072285057	3.526032	3.770909	3.789745329
4.1095668354	3.601379	3.846255	3.852534157
4.222988246	3.827419	3.940439	3.998948463
4.204151597	3.808582	3.921602	3.97811814
4.278498192	3.902765	3.878112	4.053458409
4.29833464	4.015785	4.053458	4.1232612
4.373681435	4.147642	4.091132	4.204151597
4.411354732	4.279498	4.147642	4.279498192